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Piotr Chomczynski

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EXAMINER

BABIC, CHRISTOPHER M

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



## **DETAILED ACTION**

### ***Status of the Claims***

Claim(s) 29, 30, 32-39, 41, 44, 46-52, and 59-63 are pending. The following Office Action is in response to Applicant's communication dated October 31, 2008.

### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on July 14, 2009 was filed after the mailing date of the NON-FINAL Office Action on March 6, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### ***Claim Objections***

Claims objected to because of the following informalities:

(a) With regard to claims 29, 30, 32-39, 41, 46, 52, and 61, Applicant should amend "an aqueous phases" to --an aqueous phase-- in step (c) to provide for appropriate English.

(b) Claims 32-34 depend from canceled claim 31.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112 - Indefiniteness - Maintained***

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claim(s) 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The term "higher" in is a relative term which renders the claim indefinite. The term "higher" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

#### **Response to Arguments**

Applicant's arguments have been fully considered but they are not persuasive.

Applicant points to a definition in the specification that includes the phrase, "greater than about" (see remarks pg 13). It is vague and indefinite what is meant by the phrase "greater than about." The phrase "greater than" typically indicates a minimum point. The phrase "greater than about" however, is controverted by the term "about" which implies values above and below the recited amount of molecular weight. In *Amgen, inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of--at

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least about 160,000--was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

Thus, the rejection is maintained.

***Claim Rejections - 35 USC § 103 - Withdrawn***

Upon further review of the prosecution history as well as Applicant's claim amendments and supplemental remarks (see remarks dated June 8, 2009, pg. 14-16), the rejection of claim(s) 29, 30, 39, 41, 46, 52, and 59-61 over Chen and Chomczynski is withdrawn. Neither Chen nor Chomczynski teach or suggest maintenance of the claimed pH range during introduction of a hydrophobic solvent and subsequent RNA extraction or RNA precipitation.

***Claim Rejections - 35 USC § 103 - Maintained***

It is noted that the claim below does not require maintaining the pH of the biological sample during RNA precipitation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**Claim(s) 47, 51, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (Chinese patent 1,220,995, translation provided) in view of Chomczynski (U.S. 5,346,994), and in further view Focus (1998) 20(2):36.**

Chen teaches a method for isolating purified RNA from a biological sample of (see page 3, bottom half, for example or page 4) comprising: a) treating the sample comprising phenol at a final concentration ranging from about 10% w/w to about 60% w/w and at least one ribonuclease inhibitor (see page 6, where 12-46% phenol is used in conjunction with guanidine isothiocyanate, an RNase inhibitor and see page 8, preferred embodiment 2, step 1, where the phenol reagent with 30% w/w is added to the tissue), b) mixing the sample with at least one hydrophobic solvent and a buffer at a concentration sufficient to maintain a pH in the range from about pH 3.6 to below pH 4.0 (see page 8, preferred embodiment 2, where the pH of the phenol reagent is pH 3.5, which is about 3.6 and where the hydrophobic solvent chloroform/isoamyl alcohol is added to the solution. Further note that Chen teaches overlapping ranges of pH from 3.5 to 6.5 and the use of glacial acetic acid to regulate the pH value (see page 3)), c) recovering the purified RNA from an aqueous phase to which about an equal volume of a water soluble organic solvent is added to precipitate the purified RNA (See page 8, preferred embodiment 2, where the aqueous phase is precipitated with isopropanol), d) washing and solubilizing the precipitated RNA

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(see page 9, where the RNA precipitate is washed with alcohol and dissolved in a buffer).

While Chen teaches the use of a pH adjusting component, Chen does not state that the amount used will be sufficient to maintain pH.

Chomczynski teaches the use of a pH adjusting component in an RNA solvent solution where "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)."

Neither Chen nor Chomczynski expressly teach sedimenting the sample prior to the addition of the phase separation agent.

Focus teaches that an intermediate centrifugation step, prior to the addition of chloroform, will remove undesired polysaccharides and genomic DNA.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the isolation buffer of Chen, who notes a desire to "regulate the pH value (see page 3)", to incorporate enough buffering component as taught by Chomczynski since Chomczynski notes "the solvent solution may include a buffering component, such as sodium acetate or sodium citrate, in an amount sufficient to maintain the pH of the solution (see column 3, lines 17-22)." An practitioner of ordinary skill in the art would have been motivated to include sufficient buffering in the isolation buffer of Chen in order to maintain the pH since both Chen and Chomczynski teach and motivate the use of buffering components to maintain the pH of the solution.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the isolation buffer of Chen to perform an intermediate sedimentation step prior to addition of chloroform since Focus notes in response to the problem in RNA isolation with Trizol reagent (a reagent similar to Chen's except for the pH) that "If my tissue has a high content of proteoglycans and/or polysaccharides, what can I do to ensure that these compounds don't contaminate the RNA? (see page 36)" and the Focus response is "Centrifuge following homogenization before adding chloroform at 12,000 x G at 4 C (see page 36)". An ordinary practitioner would have been motivated to perform this centrifugation since Focus notes that the centrifugation will "pellet polysaccharides (also pellets genomic DNA)", so that the centrifugation step will enhance the purity and separation of the RNA from contaminating genomic DNA, as desired by Chen.

### **Response to Arguments**

Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the proposed combination of purification steps would yield a pure RNA sample.



With specific regard to use of DNase I, the claimed invention is recited "comprising" or open language which allows for inclusion of outside steps.

Thus, the rejection is maintained.

### ***Allowable Subject Matter***

Claims 29, 30, 32-39, 41, 46, 52 would be allowable if rewritten or amended to overcome the objections.

Claims 59-61 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, and objection set forth in this Office action.

Claims 48-50 are allowable.

### ***Conclusion***

**Claims 29, 30, 32-39, 41, 46, 47, 51, 52, and 59-61 are objected to and/or rejected.**

**Claims 44, 48-50, 62, and 63 are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory

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action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christopher M. Babic/  
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